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16. ABSTRACT

A follow-up study of slow cortical potentials in children with elevated blood lead (PbB) histories was conducted two years after initial evaluation. An age x PbB interaction was again observed wherein slow wave (SW) voltage varied as a linear function of PbB with the slope of the function dependent on age. The linear relationship of SW voltage and PbB was significant using either original PbB values, (14-55 μg/dl), follow-up values (11-39 μg/dl), or the mean of the two PbB values. No evidence of a threshold for this effort was observed. The similarity of results obtained at initial and follow-up assessments suggests that the observed alterations in CNS function are persistent, despite a significant decrease in mean PbB across time. The observed change in SW voltage at PbB levels previously considered to be harmless suggests the need to reconsider the currently accepted 30 μg/dl threshold for undue lead absorption in children.

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Effects of Low to Moderate Lead Exposure on Slow Cortical Potentials in Young Children: Two Year Follow-up Study[1,2]

D. OTTO,*¶ V. BENIGNUS,*† K. MULLER,‡ C. BARTON,† K. SEIPLE,§ J. PRAH*† AND S. SCHROEDER¶

**U.S. Environment Protection Agency, Health Effects Research Laboratory Neurotoxicology Division, Research Triangle Park, NC 27711*
†Department of Psychology, ‡Department of Biostatistics and §Department of Epidemiology
¶Biological Sciences Research Center, University of North Carolina, Chapel Hill, NC 27514

OTTO, D., V. BENIGNUS, K. MULLER, C. BARTON, K. SEIPLE, J. PRAH AND S. SCHROEDER. *Effects of low to moderate lead exposure on slow cortical potentials in young children: Two year follow-up study.* NEUROBEHAV TOXICOL TERATOL 4(6) 733–737, 1982.—A follow-up study of slow cortical potentials in children with elevated blood lead (PbB) histories was conducted two years after initial evaluation. An age × PbB interaction was again observed wherein slow wave (SW) voltage varied as a linear function of PbB with the slope of the function dependent on age. The linear relationship of SW voltage and PbB was significant using either original PbB values, (14–55 μg/dl), follow-up values (11–39 μg/dl), or the mean of the two PbB values. No evidence of a threshold for this effect was observed. The similarity of results obtained at initial and follow-up assessments suggests that the observed alterations in CNS function are persistent, despite a significant decrease in mean PbB across time. The observed change in SW voltage at PbB levels previously considered to be harmless suggests the need to reconsider the currently accepted 30 μg/dl threshold for undue lead absorption in children.

Lead neurotoxicity Slow cortical potentials Central nervous system function Children

CHILDREN are known to be more susceptible than adults to nervous system impairment from lead (Pb) exposure [12]. Factors that predispose the child to risk include: (1) increased vulnerability of the immature brain particularly during the "growth spurt" period that encompasses the first three or four years of life [5]; (2) a five-fold greater absorption rate of ingested Pb in children compared to adults [2]; (3) the tendency of children under age three to ingest nonfood substances including dust, dirt and paint chips that contain Pb; and (4) the prevalence of dietary iron and calcium deficiencies, known to increase Pb absorption, in children from low income families [1].

Evidence of irreversible central nervous system damage in children with body lead burdens in excess of 80 μg/dl is incontrovertible [13], but the no-CNS-effect threshold level remains in question. The Center for Disease Control (1978) defined four classes of lead exposure in terms of blood lead (PbB) and erythrocyte protoporphyrin (EP) levels. In the CDC system Class I (normal) is defined as EP below 50 μg/dl and PbB below 30 μg/dl. Mounting evidence reviewed by Needleman [8] however, suggests that CNS effects occur in varying degree across a broad continum of lead exposure—i.e., there may be no "safe" threshold below which no deleterious effects occur.

Recent evidence from our laboratory [3,10] suggests that body lead burdens as low as 15 μg/dl systematically alter the electrical activity of the brain in young children. We found that slow wave voltage during sensory conditioning varied as a linear function of blood lead level (PbB) within an observed range of 6 to 59 μg/dl. We also found that interhemispheric gain, a measure derived from EEG spectrum analysis, varied as a cubic function of PbB across the same range of exposure. While the precise functional significance of these experimental measures remains to be determined, the results

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[2]Although this report has been approved for publication by the U.S. Environmental Protection Agency, it does not necessarily reflect the views of the Agency and no official endorsement should be inferred.

TABLE 1

DEMOGRAPHIC CHARACTERISTICS AND BLOOD LEAD LEVELS (μg/dl) OF CHILDREN IN TWO-YEAR FOLLOW-UP SAMPLE

	Age in Months		Sample Mean (Standard Error)
	35–66	67–95	
N(Male, Female)	16(11,5)	12(8,4)	
Original Blood Level (PbB1)	31.4	33.8	32.5 (2.4)
Follow-up Blood Level (PbB2)	21.5	20.5	21.1 (1.4)
Original Child IQ	90.1	83.4	87.1 (2.5)
Follow-up Child IQ	80.5	85.7	82.8 (1.8)
Socio-Economic Status	67.3	62.7	65.2 (1.5)

TABLE 2

MULTIVARIATE REGRESSION ANALYSIS OF AGE, BLOOD LEAD LEVEL (PbB1), AND SLOW WAVE VOLTAGE DURING SENSORY CONDITIONING

Source	*df*(num, den)	F	$p<$
Overall Multivariate test	6,46	3.05	0.014
All trials (1–100)			
Age	1,24	0.56	0.47
PbB1	1,24	6.97	0.015
Age × PbB1 Interaction	1,24	4.60	0.05
Early trials (1–40)			
Age	1,24	0.38	0.55
PbB1	1,24	0.09	0.76
Age × PbB1 Interaction	1,24	0.02	0.90
Late trials (41–100)			
Age	1,24	2.64	0.12
PbB1	1,24	6.23	0.02
Age × PbB1 Interaction	1,24	6.39	0.02

provide *direct* evidence of altered CNS function at the lowest PbB levels ever reported.

Do the effects of early lead exposure in children persist over time? In order to answer this question with respect to slow wave voltage, a subset of the sample described by Otto *et al.* was brought back for a two-year follow-up assessment. Several minor changes in procedures were made to clarify previous results: (1) more trials were recorded in the sensory conditioning paradigm to improve the signal-to-noise ratio of slow potential averages and to elaborate temporal features of sensory conditioning; and (2) a video cassette system was used in lieu of a movie projector to present cartoons.

METHOD

Subjects

Twenty-eight children (19 boys) aged 35 to 95 months participated in this study. Each of these children was evaluated two years earlier as part of a comprehensive lead screening program [6, 7, 10]. Demographic characteristics, PbB levels, and IQs of these children are summarized in Table 1. Mean PbBs and IQs are provided for the original and follow-up evaluations. The ranges of PbB levels were 14–55 μg/dl in the original study and 11–39 μg/dl in the follow-up study. Only three children were found to have PbBs>30 μg/dl at follow-up.

PbB Measurement

PbB levels were obtained from venipuncture blood samples taken on the day of evaluation. PbB levels were analyzed by flame atomic absorption spectrometry using the Delves-cup method [4].

Data Collection

Silver-silver chloride electrodes were used to record EEG from F_z, C_z, P_z, P_3, P_4 referred to linked mastoids. Vertical eye movements were recorded from electrodes above and below the left eye. EEG was low-pass filtered at 30 Hz (3 db down) using amplifiers modified to yield an 8-sec time constant. Data were digitized on-line at 128 Hz using a PDP-12 computer. Single trial data were plotted for visual editing. Trials with eye movements, blinks, blocking, muscle or other artifacts were eliminated from averages computed off-line.

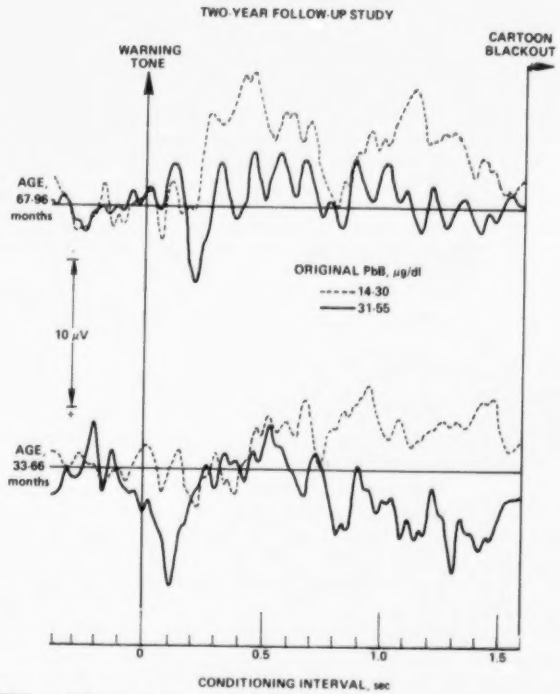

FIG. 1. Effects of age and PbB levels on slow wave voltage during passive sensory conditioning. Summary averages of all artifact-free late trials (41–100) were constructed for children in two age groups at PbB levels above and below 30 μV/dl. PbB levels from original evaluation two years earlier were used for selective averaging.

Testing Environment

Testing facilities and procedures were the same as previously described [10] except that a Panasonic Video Cassette

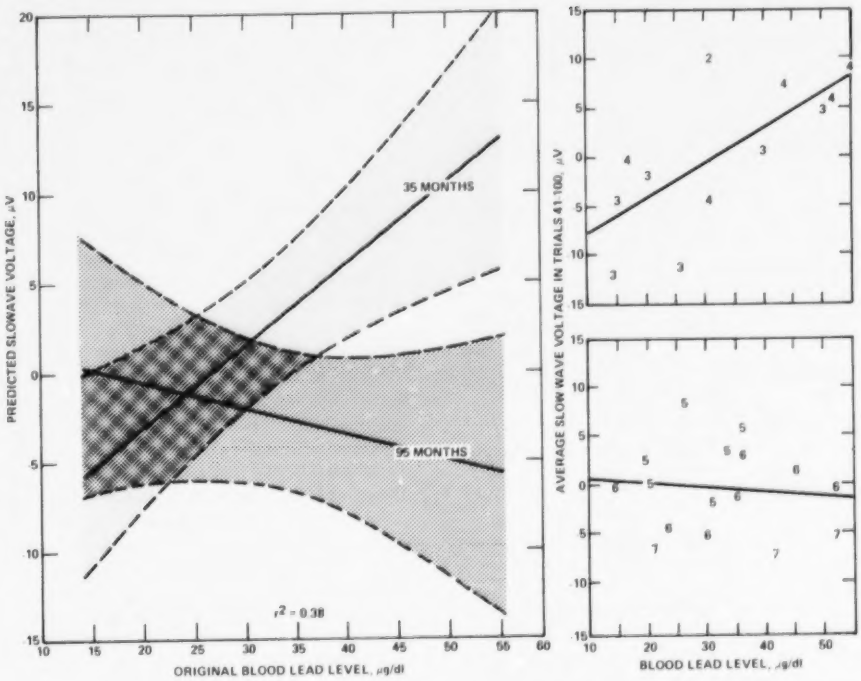
PREDICTED SLOWAVE VOLTAGE, μV
35 MONTHS
95 MONTHS
r² = 0.38
ORIGINAL BLOOD LEAD LEVEL, μg/dl
AVERAGE SLOW WAVE VOLTAGE IN TRIALS 41-100, μV
BLOOD LEAD LEVEL, μg/dl

FIG. 2. Predicted SW voltage and 95% confidence bounds in 35- and 95-month old children as a function of original PbB levels. Upper right: scatter plots and computed regression line of SW data for children aged 35–59 months. Numbers represent the age in years of children represented by individual data points. Lower right: scatter plots and computed regression line for children aged 60–95 months. These plots illustrate the linear interaction of PbB and age.

system (mod. NV-2120) and Panasonic Color TV (mod. CT-911M) were used in place of a movie projector to present cartoons. The 45 cm (diagonal) screen was located 1 m in front of subjects.

Stimulus Paradigm

Each child completed a passive sensory conditioning paradigm that was modified slightly from the original. A 100 msec 2 kHz tone served as conditioned stimulus. 1.6 sec after tone onset the TV screen was blanked for 1.5 sec (unconditioned stimulus). The intertrial interval varied pseudorandomly from 9 to 15 sec. One hundred trials were presented to each child in a 25 min period.

Data Analysis

Slow wave (SW) amplitude was computed as the mean voltage of a 1 sec interval from 500 to 1500 msec after tone onset. The mean voltage of a 350 msec pre-tone interval served as baseline. Stepwise multivariate linear regression methods were used for statistical analysis. *A priori* tests were run only on vertex data to maximize the power of tests with an overall α-level of 0.05.

RESULTS

Table 2 shows the results of the confirmatory multivariate analysis of slow wave voltage recorded at the vertex. SW voltage was regressed on PbB values obtained in the original study, designated PbB1, in order to determine if there was any residual effect of early exposure. A significant age-by-PbB1 interaction was observed in SW measures derived from individual averages across all artifact-free trials (1–100). The main effect of PbB1, but not of age, was also significant. The data were then broken down into early (1–40) and late (41–100) trials to assess the time course of the overall effect. This breakpoint was chosen to obtain approximately equal numbers of trials in early and late averages—i.e., more artifact trials were rejected in trials 51–100 than 1–50. This analysis revealed that the effects were present in the late trials only.

Figure 1 illustrates the interactive effects of age and PbB1 on SW voltage. In order to construct summary averages, children were arbitrarily divided into two age groups (35–66 months and 67–96 months) and two PbB levels (14–30 μg/dl and 31–55 μg/dl). Slow potentials in the younger group are shown in the bottom tracings: the lower PbB group shows negative SW voltage, while the higher PbB group shows positive SW voltage. The older low-PbB group (upper tracings) show somewhat larger negative slow potentials while the older high PbB children have depressed negative slow waves.

Figure 2 shows predicted SW voltage and 95% confidence bands plotted as a function of original PbB levels for the extreme ages represented in the follow-up sample. Scatter

TABLE 3

SUMMARY OF RESULTS OF MULTIVARIATE REGRESSION ANALYSES USING PbB1, PbB2, AND (PbB1 + PbB2)/2

Source	*df*(num, den)	F	$p<$
Overall Tests			
PbB1	6,46	3.05	0.014
PbB2	6,46	2.26	0.055
(PbB1 + PbB2)/2	6,46	3.30	0.009
Late Trials (41–100)			
PbB1	1,24	6.23	0.02
PbB2	1,24	4.82	0.04
(PbB1 + PbB2)/2	1,24	6.61	0.017
Age × PbB1 Interaction	1,24	6.39	0.02
Age × PbB2 Interaction	1,24	3.83	0.07
Age × (PbB1 + PbB2)/2 Interaction	1,24	7.22	0.013

plots of SW values for individual subjects aged 35–59 months (upper right) and 60–95 months (lower right) are also shown. The linear model derived from this sample projects that the slope of the age × PbB interaction function passes through zero between ages six and seven.

Mean blood lead levels dropped from 32.5 μg/dl to 21.1 μg/dl during the two-year period between initial and follow-up evaluations (Table 1). In view of this substantial decrease, it was of interest to determine if a significant age × PbB interaction was present if SW voltage was regressed against follow-up blood lead levels. Several *post hoc* exploratory analyses were run to examine this question. Table 3 indicates that the main effect of PbB2 was significant ($p<0.04$), but that the interaction of age and PbB2 values was marginal ($p<0.07$). A third analysis was run using mean blood lead levels (Pbb1+PbB2)/2 that represent an integrated index of body lead burden over time. Results of this analysis, summarized in Table 3, also reflect a significant age × PbB interaction ($p<0.017$). Since these analyses were unplanned, p-values should be interpreted as lower bounds of actual probabilities.

Correlation coefficients were computed (Table 4) for IQ, PbB, early and late SW measures in order to explore further the interrelationship of these variables. This table depicts an interesting disassociation of SW, IQ and PbB measures. SW voltage correlated significantly with child IQ during early, but not late trials. Conversely, PbB1, and PbB2, and mean PbB correlated significantly with SW voltage during late, but not early trials. Neither child IQ nor maternal IQ correlated with any PbB measure.

DISCUSSION

The primary question addressed in the follow-up study was whether alteration in CNS function related to elevated body lead burden in young children persist over time. Twenty-eight children from a high risk, previously exposed population were re-evaluated after a two-year period. Although the mean PbB levels of the childen decreased by more than 11 μg/dl at follow-up, the same basic linear relationship of SW voltage, age, and body Pb burden observed previously was again found. That is, SW voltage recorded in children during passive sensory conditioning varied as a linear function of PbB. The slope of the SW × PbB function, moreover, varied systematically with age.

Of particular interest was the fact that the linear relationship of SW voltage and PbB pertained whether PbB values from the initial or two-year follow-up evaluation were used. Demonstration of altered CNS function relative to original PbB values suggests a change that persists over time. Demonstration of effects relative to current PbB levels that were much lower overall and that varied within a much narrower range reinforces the continuum concept that Pb exposure at any level produces a graded effect on CNS function. The observation of systematic changes within a 11–39 μg/dl range raises further question about the validity of the widely accepted 30 μg/dl "safe" threshold, particularly in young children. In the present case, of course, we know that many of the children in the sample previously had higher PbB levels that apparently have produced persistent alterations in CNS function. The recent report of decreased IQ in children with PbB levels below 30 μg/dl [14] supports the findings of Needleman *et al.* [9] and others of CNS effects at body burdens previously considered to be harmless. Current conceptions concerning the existence of a "safe threshold" for body lead burden clearly must be re-examined. The continuum theory, furthermore, poses a challenge to government agencies charged with establishing environmental standards or "threshold limit values" since such standards are predicated on the existence of exposure thresholds that will not endanger human health.

The foregoing implies that we have precisely replicated our previous findings. Such is not the case. In the first place,

TABLE 4

TWO-YEAR FOLLOW-UP STUDY: CORRELATIONS OF BODY LEAD BURDEN (PbB), SLOW WAVE VOLTAGE (SW), CHILD IQ (IQ_c), AND MATERNAL IQ (IQ_m)

N=28	PbB1	PbB2	Mean PbB	SW_{1-40}	SW_{41-100}	SW_{1-100}	IQ_c
PbB2	.64*						
Mean PbB	.95*	.84*					
SW_{1-40}	.08	.03	.06				
SW_{41-100}	.04	.45‡	.45‡	−.46‡			
SW_{1-100}	.44‡	.45‡	.49†	.55†	.49†		
IQ_c	−.27	−.13	−.24	−.40§	−.16	−.54†	
IQ_m	−.06	.03	−.03	.07	−.08	−00	.26

*$p<0.001$, †$p<0.01$, ‡$p<0.02$, §$p<0.05$.

replication requires an independent sample that cannot be satisfied by a follow-up study, even though electrophysiological data from only 12 of 28 subjects in the follow-up sample were actually used in the original analysis. (Data from only about 25 percent of children aged 13 to 30 months met the electrophysiological data analysis criteria for acceptance in the original study). Secondly, the slope of the age × PbB functions observed in the follow-up study appears to be reversed from earlier data. Consideration of temporal changes provides a likely explanation of this difference. Only 35 trials were presented in the original study, while 100 trials were presented in the follow-up study. The original data thus correspond roughly to the "early" trial data in the present study. The age × PbB interaction was observed only in late trials (41–100) in the follow-up study, perhaps due to the reduced sample size. The inverse correlation of SW voltage between early and late trials (Table 4), however, indicates that polarity tended to reverse between early and late trials. This temporal inversion of SW polarity is consistent with the slope differences noted between original and follow-up studies.

Further research is needed to clarify the temporal dynamics of slow potential changes during sensory conditioning in children with varying body lead burdens. Results of the follow-up study, however, add important new information to the growing body of evidence that lead exposure alters CNS function across a broad continuum of values. The critical finding is that CNS alterations in young children appear to persist across time even after blood lead levels are substantially reduced. Further discussion of the implications and limitations of these data is presented elsewhere [11].

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